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(54) Title: METHOD FOR TREATING ANGINA

(57) Abstract: A method for administering a ranolazine dosage formulations to treat patients suffering from angina who are also suffering from a second complication or disease such a heart disease and diabetes and also to reduce myocardial infarct size wherein the infarcts is the result of an ischemic event.

TITLE: Method For Treating Angina

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BACKGROUND OF THE INVENTION**1. Field of the Invention**

This invention relates to methods for using ranolazine dosage formulations to treat patients suffering from angina who are also suffering from a second complication or disease such a heart disease and diabetes. This invention also relates to a method for reducing myocardial infarct size by administering ranolazine to a mammal prophalactically or by
10 administering ranolazine to a mammal suffering from a heart attack.

2. Description of the Art

U.S Patent No. 4,567,264, the specification of which is incorporated herein by reference, discloses ranolazine, (\pm)-N- (2,6-dimethylphenyl)-4-[2-hydroxy-3- (2-
15 methoxyphenoxy)-propyl]-1-piperazineacetamide, and its pharmaceutically acceptable salts, and their use in the treatment of cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction.

U.S. Patent No. 5,506,229, the specification of which is incorporated herein by reference, discloses the use of ranolazine and its pharmaceutically acceptable salts and esters
20 for the treatment of tissues experiencing a physical or chemical insult, including cardioplegia, hypoxic or reperfusion injury to cardiac or skeletal muscle or brain tissue, and for use in transplants. Conventional oral and parenteral formulations are disclosed, including controlled release formulations. In particular, Example 7D of U.S. Patent No. 5,506,229 describes a controlled release formulation in capsule form comprising microspheres of ranolazine and
25 microcrystalline cellulose coated with release controlling polymers.

The presently preferred route of administration for ranolazine and its pharmaceutically acceptable salts and esters is oral. A typical oral dosage form is a compressed tablet, a hard gelatin capsule filled with a powder mix or granulate, or a soft gelatin capsule (softgel) filled with a solution or suspension. U.S. Patent No. 5,472,707, the specification of which is
30 incorporated herein by reference, discloses a high-dose oral formulation employing supercooled liquid ranolazine as a fill solution for a hard gelatin capsule or softgel.

It was recently discovered that ranolazine can be used to treat angina in humans for a sustained period of time. See U.S. patent application serial numbers 09/520,932, 09/321,522,

and 09/538,337, the specifications of each of which are incorporated herein by reference. However, it remains uncertain whether or not ranolazine has additional therapeutic benefits or whether or not ranolazine can be used to treat patients suffering from angina and a second disease which might be detrimentally impacted ranolazine.

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SUMMARY OF THE INVENTION

It is an object of this invention to provide methods for treating mammals and especially humans with ranolazine where the humans suffer from a second disease in addition to variant or exercised induced angina.

Another aspect of this invention is a method for treating mammals and especially
10 humans prophylactically with ranolazine to reduce infarct size.

Still another aspect of this invention is a method for treating mammals and especially humans who have recently experienced a heart attack with ranolazine in order to reduce infarct size.

One method of this invention includes treating a mammal suffering from angina and
15 at least one second disorder by administering a dose of a pharmaceutical dosage form to the mammal including ranolazine and at least one pharmaceutical excipient. In this method, the second disorder is preferably heart disease or diabetes and the mammal is human.

Another method of this invention includes reducing myocardial infarct size in a mammal by administering a dose of a pharmaceutical dosage form to the mammal including
20 ranolazine and at least one pharmaceutical excipient. In this method, the pharmaceutical dosage form may be administered before, during, or after the mammal experiences an ischemic event and the mammal is preferably a human.

DESCRIPTION OF CURRENT EMBODIMENTS

This invention includes methods for administering ranolazine to mammals, and especially to humans, in order to reduce infarct size and in order to treat humans suffering angina and at least one second disorder.

5 Before discussing the methods of this invention, several of the terms used in the specification and claims will be defined.

"Ranolazine" is the compound (\pm)-N- (2,6-dimethylphenyl)-4-[2-hydroxy-3- (2-methoxyphenoxy) propyl]-1-piperazine-acetamide, or its enantiomers (R)-(+)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazineacetamide, and
10 (S)-(-)-N-(2,6-dimethylphenyl) -4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazineacetamide and their pharmaceutically acceptable salts, and mixtures thereof. Unless otherwise stated the ranolazine plasma concentrations used in the specification and examples refers to ranolazine free base.

"Optional" and "optionally" mean that the subsequently described event or
15 circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional pharmaceutical excipients" indicates that a formulation so described may or may not include pharmaceutical excipients other than those specifically stated to be present, and that the formulation so described includes instances in which the optional excipients are present and
20 instances in which they are not.

"Treating" and "treatment" refer to any treatment of a disease in a mammal, particularly a human, and include:

- (i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;
- 25 (ii) inhibiting the disease, i.e., arresting its development; or
- (iii) relieving the disease, i.e., causing regression of the disease.

"Immediate release" ("IR") refers to formulations or dosage units that rapidly dissolve *in vitro* and are intended to be completely dissolved and absorbed in the stomach or upper gastrointestinal tract. Conventionally, such formulations release at least 90% of the active
30 ingredient within 30 minutes of administration.

"Sustained release" ("SR") refers to formulations or dosage units of this invention that are slowly and continuously dissolved and absorbed in the stomach and gastrointestinal tract

over a period of about six hours or more. Preferred sustained release formulations are those exhibiting plasma concentrations of ranolazine suitable for no more than twice daily administration with two or less tablets per dosing as described below.

“Angina” refers to variant or exercised induced angina. Exercise induced angina is sometimes referred to as stable angina while variant angina is sometimes referred to as unstable angina.

“Second disorder” refers to a physiological abnormality. In a preferred embodiment, the disorder is diabetes or congestive heart failure (CHF).

“Plasma ranolazine concentration” is a mean concentration determined by analyzing the concentration of ranolazine in as few as five to as many as ten humans who are on the same dosing schedule. It is important that the ranolazine concentration is a mean value because of variances in ranolazine concentrations in individuals that may be caused by differences in weight, metabolism, or disease states which may cause one person to metabolize ranolazine faster or slower than an average person. The plasma ranolazine levels are determined from drawn blood onto heparin.

Definitions of other terms used in this application are:

ANOVA = analysis of variance

ATP = adenosine triphosphate

ECG = electrocardiographic

ETT = exercise treadmill test

PDH = pyruvate dehydrogenase

C_{\max} = maximum concentration

C_{trough} = residual concentration at 8 hours post-dose for IR formulations and 12 hours post-dose for SR formulations A-C of Example 2.

tid = three times per day

bid = twice daily

C_x = concentration at time x

T_{\max} = time to maximum concentration

AUC_x = area under the curve after x hours or time interval

Percentages given are percentages by weight, unless otherwise stated. This invention involves sustained release ranolazine dosage forms as well as methods for administering

sustained release ranolazine dosage forms of this invention to provide for therapeutic plasma levels of ranolazine.

Ranolazine is a partial fatty acid oxidation (pFOX) inhibitor that shifts ACP production towards more oxygen efficient glucose oxidation. Because of a metabolic shift
5 towards glucose oxidation, and away from fatty acid oxidation, there were concerns that ranolazine could detrimentally effect a second disorder experienced by a mammal and especially human in addition to variant or exercise induced angina. For example, since ranolazine encourages the heart to oxidize glucose, ranolazine might be less effective for treating angina in patients suffering from diabetes because of difficulties in maintaining
10 serum glucose levels. Additionally, it was unknown whether ranolazine would exacerbate the symptoms of diabetes or congestive heart failure in those mammals and especially humans suffering from both angina and a second disorder.

The Applicants have surprisingly determined that ranolazine is effective when administered to humans suffering from angina and a second disorder such as diabetes or
15 congestive heart failure. The patients suffering from angina and a second disorder are treated with ranolazine in the same manner as those patients who suffer from angina alone. Typically, the ranolazine will be administered in an oral dosage form where the dose is one or two tablets of ranolazine and where the dose is administered once, twice or three times a day or more.

20 The oral dosage form used is preferably a sustained release dosage form as described below. In addition, the dosage form is dosed in a manner that maintains human plasma ranolazine levels within the ranges and within the peak to trough plasma ranolazine levels set forth below as well.

It is anticipated that there may be instances where it may desirable to administer
25 ranolazine for sustained period of time by using a dosage form other than an oral dosage form. Such dosage forms may take the form, for example, of an intravenous solution including ranolazine, a bolus injection including ranolazine, an inhaled dosage form, a dermal patch, eye drops, a topical cream, suppositories, powders, solutions, suspensions, emulsions, aerosols, ointments, and by any other methods and dosage forms known in the art for
30 administering a pharmaceutical composition to a mammal.

It is preferred that the ranolazine dosage form that is administered in the method for treating mammals suffering from angina and from a second disorder is a sustained release dosage form.

Useful sustained release ranolazine formulations are preferably in the form of a compressed tablet comprising an intimate mixture of ranolazine and a partially neutralized pH-dependent binder that controls the rate of ranolazine dissolution in aqueous media across the range of pH in the stomach (typically approximately 2) and in the intestine (typically approximately about 5.5).

To provide for a sustained release of ranolazine, one or more pH-dependent binders are chosen to control the dissolution profile of the ranolazine formulation so that the formulation releases ranolazine slowly and continuously as the formulation passed through the stomach and gastrointestinal tract. The dissolution control capacity of the pH-dependent binder(s) is particularly important in a sustained release ranolazine formulation because a sustained release formulation that contains sufficient ranolazine for twice daily administration may cause untoward side effects if the ranolazine is released too rapidly ("dose-dumping").

Accordingly, the pH-dependent binders suitable for use in this invention are those which inhibit rapid release of drug from a tablet during its residence in the stomach (where the pH is below about 4.5), and which promotes the release of a therapeutic amount of ranolazine from the dosage form in the lower gastrointestinal tract (where the pH is generally greater than about 4.5). Many materials known in the pharmaceutical art as "enteric" binders and coating agents have the desired pH dissolution properties. These include phthalic acid derivatives such as the phthalic acid derivatives of vinyl polymers and copolymers, hydroxyalkylcelluloses, alkylcelluloses, cellulose acetates, hydroxyalkylcellulose acetates, cellulose ethers, alkylcellulose acetates, and the partial esters thereof, and polymers and copolymers of lower alkyl acrylic acids and lower alkyl acrylates, and the partial esters thereof.

Preferred pH-dependent binder materials which can be used in conjunction with ranolazine to create a sustained release formulation are methacrylic acid copolymers. Methacrylic acid copolymers are copolymers of methacrylic acid with neutral acrylate or methacrylate esters such as ethyl acrylate or methyl methacrylate. A most preferred copolymer is methacrylic acid copolymer, Type C, USP (which is a copolymer of methacrylic acid and ethyl acrylate having between 46.0% and 50.6% methacrylic acid units). Such a

copolymer is commercially available, from Röhm Pharma as Eudragit® L 100-55 (as a powder) or L30D-55 (as a 30% dispersion in water). Other pH-dependent binder materials which may be used alone or in combination in a sustained release ranolazine dosage form include hydroxypropyl cellulose phthalate, hydroxypropyl methylcellulose phthalate, 5 cellulose acetate phthalate, polyvinylacetate phthalate, polyvinylpyrrolidone phthalate, and the like. One or more pH-dependent binders are present in the ranolazine dosage forms of this invention in an amount ranging from about 1 to about 20 wt%, more preferably from about 5 to about 12 wt% and most preferably about 10 wt%. One or more pH-independent binders may be in used in sustained release ranolazine oral dosage forms. It is to 10 be noted that pH-dependent binders and viscosity enhancing agents such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth)acrylate esters, and the like, do not themselves provide the required dissolution control provided by the identified pH-dependent binders. The pH-independent binders are present in the formulation of this invention in an amount ranging from about 1 to about 10 15 wt%, and preferably in amount ranging from about 1 to about 3 wt% and most preferably about 2.0 wt%.

As shown in Table 1, ranolazine is relatively insoluble in aqueous solutions having a pH above about 6.5, while the solubility begins to increase dramatically below about pH 6.

Table 1

Solution pH	Solubility (mg/mL)	USP Solubility Class
4.81	161	Freely soluble
4.89	73.8	Soluble
4.90	76.4	Soluble
5.04	49.4	Soluble
5.35	16.7	Sparingly soluble
5.82	5.48	Slightly soluble
6.46	1.63	Slightly soluble
6.73	0.83	Very slightly soluble
7.08	0.39	Very slightly soluble
7.59 (unbuffered water)	0.24	Very slightly soluble
7.73	0.17	Very slightly soluble
12.66	0.18	Very slightly soluble

20 Increasing the pH-dependent binder content in the formulation decreases the release rate of ranolazine from the formulation at pH is below 4.5 typical of the pH found in the stomach. The enteric coating formed by the binder is less soluble and increases the relative release rate

above pH 4.5, where the solubility of ranolazine is lower. A proper selection of the pH-dependent binder allows for a quicker release rate of ranolazine from the formulation above pH 4.5, while greatly affecting the release rate at low pH. Partial neutralization of the binder facilitates the conversion of the binder into a latex like film which forms around the individual ranolazine granules. Accordingly, the type and the quantity of the pH-dependent binder and amount of the partial neutralization composition are chosen to closely control the rate of dissolution of the ranolazine from the formulation.

The dosage forms of this invention should have a quantity of pH-dependent binders sufficient to produce a sustained release formulation from which the release rate of ranolazine is controlled such that at low pHs. (below about 4.5) the rate of dissolution is significantly slowed. In the case of methacrylic acid copolymer, type C, USP (Eudragit® L 100-55), a suitable quantity of pH-dependent binder is between 5% and 15%. The pH dependent binder will typically have from about 1 to about 20% of the binder methacrylic acid carboxyl groups neutralized. However, it is preferred that the degree of neutralization ranges from about 3 to 6%.

The sustained release formulation may also contain pharmaceutical excipients intimately admixed with the ranolazine and the pH-dependent binder. Pharmaceutically acceptable excipients may include, for example, pH-independent binders or film-forming agents such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth)acrylate esters (e.g. the methyl methacrylate/ethyl acrylate copolymers sold under the trademark Eudragit® NE by Röhm Pharma), starch, gelatin, sugars, carboxymethylcellulose, and the like. Other useful pharmaceutical excipients include diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like; surface active agents such as polyoxyethylene sorbitan esters, sorbitan esters and the like; and coloring agents and flavoring agents. Lubricants (such as talc and magnesium stearate) and other tableting aids are also optionally present.

The sustained release ranolazine formulations of this invention have a ranolazine content of above about 50% by weight to about 95% or more by weight, more preferably between about 70% to about 90% by weight and most preferably from about 70 to about 80% by weight; a pH-dependent binder content of between 5% and 40%, preferably between 5% and 25%, and more preferably between 5% and 15%; with the remainder of the dosage form comprising pH-independent binders, fillers, and other optional excipients.

Particularly preferred sustained release ranolazine formulations consist, essentially of:

<u>Ingredient</u>	<u>Weight Range (%)</u>	<u>Preferred Range (%)</u>	<u>Most Preferred (%)</u>
Ranolazine	50-95	70-90	75
5 Microcrystalline cellulose (filler)	1-35	5-15	10.6
Methacrylic acid copolymer	1-35	5-12.5	10.0
Sodium hydroxide	0.1-1.0	0.2-0.6	0.4
Hydroxypropyl methylcellulose	0.5-5.0	1-3	2.0
Magnesium stearate	0.5-5.0	1-3	2.0

- 10 The sustained release ranolazine formulations are prepared as follows: ranolazine and pH-dependent binder and any optional excipients are intimately mixed (dry-blended). The dry-blended mixture is then granulated in the presence of an aqueous solution of a strong base which is sprayed into the blended powder. The granulate is dried, screened, mixed with optional lubricants (such as talc or magnesium stearate), and compressed into tablets.
- 15 Preferred aqueous solutions of strong bases are solutions of alkali metal hydroxides, such as sodium or potassium hydroxide, preferably sodium hydroxide, in water (optionally containing up to 25% of water-miscible solvents such as lower alcohols).

- The resulting ranolazine containing tablets may be coated with an optional film-forming agent, for identification, taste-masking purposes and to improve ease of swallowing.
- 20 The film forming agent will typically be present in an amount ranging from between 2% and 4% of the tablet weight. Suitable film-forming agents are well-known to the art and include hydroxypropyl methylcellulose, cationic methacrylate copolymers (dimethylaminoethyl methacrylate/ methyl-butyl methacrylate copolymers - Eudragit® E - Röhm Pharma), and the like. These film-forming agents may optionally contain colorants, plasticizers, and other
- 25 supplemental ingredients.

- The compressed tablets preferably have a hardness sufficient to withstand 8 Kp compression. The tablet size will depend primarily upon the amount of ranolazine in the tablet. The tablets will include from 300 to 1100 mg of ranolazine free base. Preferably, the tablets will include amounts of ranolazine free base ranging from 400-600 mg, 650-850 mg,
- 30 and 900-1100 mg.

In order to influence the dissolution rate, the time during which the ranolazine containing powder is wet mixed is controlled. Preferably the total powder mix time, *i.e.* the

time during which the powder is exposed to sodium hydroxide solution, will range from 1 to 10 minutes and preferably from 2 to 5 minutes. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer for drying at about 60°C.

Surprisingly, it has been found that these methods produce sustained release
5 ranolazine formulations that provide lower peak plasma ranolazine levels and yet effective plasma concentrations of ranolazine for up to 12 hours and more after administration, when the ranolazine used as its free base, rather than as the more pharmaceutically common ranolazine dihydrochloride salt or as another salt or ester. The use of ranolazine free base affords at least one advantage: The proportion of ranolazine in the tablet can be increased,
10 since the molecular weight of ranolazine free base is only 85% that of ranolazine dihydrochloride. In this manner, delivery of an effective amount of ranolazine is achieved while limiting the physical size of the dosage unit.

Another advantage of sustained release ranolazine formulations is that they are prepared by a process that essentially involves only water as a solvent, and utilizes standard
15 pharmaceutical processing techniques and equipment.

The sustained release ranolazine formulations can be used for treating cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction; treatment of tissues experiencing a physical or chemical insult, including cardioplegia, hypoxic or reperfusion injury to cardiac or skeletal muscle or brain tissue, and
20 ischemia; and peripheral arterial diseases, such as intermittent claudication. It is most preferred that the sustained release dosage formulation be used as a mammalian anti-anginal agent and most preferably as a human anti-anginal agent.

The oral sustained release ranolazine dosage formulations of this invention are administered one, twice; or three times in a 24 hour period in order to maintain a plasma
25 ranolazine level above the threshold therapeutic level and below the maximally tolerated levels, of between about 550 and 7500 ng base/mL in a patient. This corresponds to an amount of ranolazine 2 HCl ranging from about 644 ng/mL to about 8782 ng/mL. Furthermore, the timing of the oral ingestion of the ranolazine oral dosage forms should be controlled to insure that the plasma ranolazine level does not exceed about 7500 ng base/mL
30 and preferably so that the plasma ranolazine level does not exceed about 5000 ng base/mL and most preferably so that it does not exceed 3800 ng base/mL. In some instances it may be beneficial to limit the peak plasma ranolazine level to no more than about ng base/mL. At the

same time, the plasma trough ranolazine levels should preferably not fall below about 1000 ng base/mL, and in some instances should not fall below 1700 ng base/mL

5 In order to achieve the preferred plasma ranolazine level of from about 1000 to about 3800 ng base/mL, it is preferred that the oral ranolazine dosage forms described herein are administered once or twice daily. If the dosage forms are administered twice daily, then it is preferred that the oral ranolazine dosage forms are administered at about twelve hour intervals.

10 In addition to formulating and administering oral sustained release dosage forms of this invention in a manner that controls the plasma ranolazine levels, it is also important to minimize the difference between peak and trough plasma ranolazine levels. The peak plasma ranolazine levels are typically achieved at from about 30 minutes to eight hours or more after initially ingesting the dosage form while trough plasma ranolazine levels are achieved at about the time of ingestion of the next scheduled dosage form. It is preferred that the sustained release dosage forms of this invention are administered in a manner that allows for a peak
15 ranolazine level no more than 8 times greater than the trough ranolazine level, preferably no more than 4 times greater than the trough ranolazine and most preferably no greater than 2 times trough ranolazine level.

20 The sustained release ranolazine formulations of this invention provide the therapeutic advantage of minimizing variations in ranolazine plasma concentration while permitting, at most, twice-daily administration. The formulation may be administered alone, or (at least initially) in combination with an immediate release formulation if rapid achievement of a therapeutically effective plasma concentration of ranolazine is desired or by soluble IV formulations and oral dosage forms.

25 In another method of this invention, ranolazine is administered to a mammal and preferably to humans in order to reduce infarct size. A coronary infarct is the outcome of a loss of the supply of oxygen to the heart muscles. Ischemia can occur suddenly as in the case of a heart attack or ischemia can be gradual. Regardless the ischemic event, ranolazine is useful for reducing the size of the infarct caused by cardiac oxygen loss.

30 Ranolazine can be administered by several methods in order to reduce infarct size. In one method, ranolazine can be given prophylactically, much like aspirin therapy, to patients who have suffered a heart attack or who are at risk for suffering a heart attack. Alternatively, ranolazine can be administered to patients during or shortly after a heart attack in order to

reduce the infarct size. In another embodiment, ranolazine can be administered to patients who are in danger of or who are suffering from a cardiac ischemia for any reason.

5 The dosage form used to administer ranolazine to reduce infarct size will vary depending upon the purpose of ranolazine administration. When ranolazine is being administered as a prophalactic, then the ranolazine will be preferably administered in an oral dosage form and preferably as immediate release or sustained release capsule or tablet. However, any of the methods of administering ranolazine discussed above can be used to dose ranolazine prophalactically.

10 When ranolazine is administered to a patient suffering from an ischemic event such as a heart attack, then ranolazine will typically initially be administered intravenously or in a bolus injection to provide an immediate increase in plasma ranolazine levels. Following the initial intravenous or bolus injection, the ranolazine may continued to be administered intravenously or by bolus or the ranolazine may be administered by any of the methods and dosage forms described above.

15 When administered to reduce infarct size either prophylactically or during or subsequent to a heart attack, the ranolazine should be administered in an amount sufficient to reduce infarct size. Generally, the pharmaceutically useful amount will range from about 0.01 to about 50 mg/kg/day and preferably from between 1 to 25 mg/kg/day.

20 The following Examples are representative of the invention, but are not to be construed as limiting the scope of the claims.

EXAMPLES

These Examples detail methods for manufacturing solid dosage forms including ranolazine as well as experiments performed to evaluate the effectiveness of ranolazine administration and effectiveness. Throughout these Examples it should be noted that:

5 (1) Oral doses of the instant release (IR) formulation were given as capsules or tablets of the dihydrochloride salt and are expressed as the dihydrochloride salt.

(2) Oral doses of the sustained release (SR) formulation were given as tablets of the ranolazine base and are expressed as the base.

10 (3) When IR and SR formulations were compared in the same study, doses are expressed in terms of both base and dihydrochloride. The conversion factor for dihydrochloride to base is 0.854 (e.g.: 400 mg dihydrochloride \times 0.854 = 342 mg free base equivalent).

(4) All plasma levels and pharmacokinetic parameters are expressed as levels of free base.

15

EXAMPLE 1

This Example describes a method of preparing immediate release (IR) ranolazine formulations. Ranolazine dihydrochloride (4000 g), microcrystalline cellulose (650 g), polyvinylpyrrolidone (100 g), and croscarmellose sodium (100 g) powders were intimately
20 mixed together in a Fielder PMA 65 mixer-granulator, and sufficient water was then added, with mixing to form a granulate. The granulate was dried in an Aeromatic Strea-5 fluid bed drier, screened, and mixed with magnesium stearate (100 g). The mixture was filled into hard gelatin capsules to a fill weight of, for example, 500 mg per capsule to achieve a dose of 400 mg of ranolazine dihydrochloride (equivalent to 342 mg of ranolazine free base) per capsule,
25 but may be filled to fill weight of 30 to 400 mg of ranolazine dihydrochloride.

EXAMPLE 2

This Example describes a method of preparing sustained release (SR) ranolazine formulations.

30 A sustained release (SR) formulation, designated as SR Formulation A, and including pH-dependent and pH-independent binders was prepared by combining Ranolazine (2500 g), methacrylic acid copolymer, Type C (Eudragit® L 100-55 - Röhm Pharma) (1000 g),

microcrystalline cellulose (Avicel®) (100 g) (710 g), and polyvinyl pyrrolidinone powders were intimately mixed together in a Fielder PMA 65 mixer-granulator. The mixture was granulated with a solution of sodium hydroxide (40 g) in water, and a 30% aqueous dispersion of methyl methacrylate/ethyl acrylate copolymer (Eudragit® NE 30 D - Röhm Pharma) (1667 g) was added to the wet mass. The resulting granulate was dried in an Aeromatic Strea-5 fluid bed drier, screened, and then mixed with croscarmellose sodium (100 g) and magnesium stearate (50 g). The mixture was compressed into 684 mg tablets with a Manesty B tablet press to achieve dose of 342 mg of ranolazine free base per tablet. This formulation is referred to as SR Formulation A.

SR Formulation B was prepared in the same manner as SR Formulation A except that the Eudragit® L 100-55 was reduced to 500 g, and the Eudragit® NE 30 D was replaced by a 40% aqueous dispersion of a methyl methacrylate/ethyl acrylate copolymer (Eudragit® NE 40 D - Röhm Pharma) (2500 g). The resulting (SR) formulation included 342 mg ranolazine free base per tablet.

In SR Formulation C, ranolazine free base (342 mgs) was blended with microcrystalline cellulose and polyvinyl pyrrolinone K25, granulated with water, dried, and blended with croscarmellose sodium and magnesium stearate. The blend was compressed into tablets and coated with an enteric coating.

SR Formulation D, including only a pH dependent binder was prepared by combining Ranolazine (7500 g), Eudragit® L 100-55 (1000 g), hydroxypropyl methylcellulose (Methocel® E5 - source) (200 g), and microcrysalline cellulose (Avicel®) (1060 g) by intimate mixing. The mixed powders were granulated with a solution of sodium hydroxide (40 g) in water (1900 to 2500 grams). The granulate was dried and screened, mixed with magnesium stearate (200 g), and compressed for example into tablets weighing 667 mg to achieve a dose of 500 mg of ranolazine free base per tablet. The tablets were spray coated in a 24 inch Accelacota® cylindrical pan coater with OPADRY film coating solution to a 2-4% weight gain. OPADRY film coating solutions are available in a variety of colors from Colorcon, West Point, PA.

The stepwise procedure for preparing SR Formulation D is as follows:

- a) Blend together ranolazine, microcrystalline cellulose, methacrylate copolymer (Type C) and hydroxypropyl methyl cellulose using an appropriate blender.

- b) Dissolve sodium hydroxide in purified water.
- c) Using appropriate granulation equipment, slowly add the sodium hydroxide solution to the blend with constant mixing. Add a further aliquot of water, if necessary.
- 5 d) Continue mixing to achieve additional massing. Add a further aliquot of water, if necessary.
- e) Dry granulated in a fluid bed dryer.
- f) Screen dried granules through an appropriate mill.
- g) Add magnesium stearate to the screened granules and blend together.
- 10 h) Pass the granulated material through a chilsonator, if needed.
- i) Compress the granules into tablets using appropriately sized tooling.
- j) Disperse OPADRY powder in water and film-coat using appropriately sized coating equipment to a typical level of 2-4% by weight.
- k) Polish with carnauba wax using a typical level of 0.002-0.003% by weight.

15

EXAMPLE 3

In this Example, the safety and anti-ischemic effects of high plasma ranolazine levels in a large group of angina patients was evaluated and the duration of any effects during steady-state dosing with bid and tid regimens was assessed. In this Example, patients with chronic stable angina pectoris who were responsive to conventional antianginal drugs were treated with 3 ranolazine •2HC1 dosing regimens: 267 mg tid, 400 mg bid and 400 mg tid IR Formulations of Example 1. Exercise testing parameters and ranolazine free base concentrations were determined at peak and trough plasma levels.

Methods

25 The study involved double-blind, placebo-controlled randomized treatment phase with 4 treatments (placebo, ranolazine •2HC1 400 mg bid, ranolazine •2HC1 267 mg tid, and ranolazine •2HC1 400 mg tid), 4 treatment sequences and 5 double-blind treatment periods in an extended period Latin square design on pre-qualified patients who were responsive to known antianginal therapy and had stable exercise times.

30 Human patients with chronic stable angina pectoris, of at least 3 months' duration, that had responded to conventional antianginal therapy were considered candidates. In addition, patients had to have electrocardiographic (ECG) evidence of exercise-induced ischemia based

upon horizontal or down-sloping ST-segment depression of ≥ 1 mm that persisted in 3 consecutive beats during an exercise stress test and an ECG pattern that would not interfere with interpretation of ST-segment changes. The latter criterion specifically excluded patients with left ventricular hypertrophy, pre-excitation, conduction abnormalities, or pacemaker rhythm. Other exclusion criteria included unstable angina or myocardial infarction within the preceding 3 months, heart failure defined as New York Heart Association Class III or IV, significant valvular or congenital heart disease that was uncorrected, need for digoxin or long-acting nitrate therapy, labile diabetes mellitus, or other serious conditions that would confuse follow-up evaluation.

These immediate release ranolazine •2HCl dosing regimens (267 mg tid, 400 mg bid, 400 mg tid) and a placebo were administered during the treatment phase. Patients took one capsule containing either 267 mg or 400 mg of ranolazine dihydrochloride, or placebo at 8:00 a.m., 4:00 p.m., 8:00 p.m. and 12:00 a.m. All capsules were identical in appearance. Patients were randomized to 1 of 4 treatment sequences, with 25% of the patients assigned to each sequence. Each treatment was administered for 1 week, with one treatment repeated during a fifth 1-week period.

To qualify patients receiving their usual antianginal medications underwent a screening exercise treadmill test (ETT-1) using a Sheffield modified Bruce protocol. If the time to onset angina was ≥ 3 but ≤ 13 minutes, an antianginal drug was withdrawn and treatment with single-blind placebo was initiated. After 1 to 2 weeks, patients returned for another ETT (ETT-2). If the time to onset angina decreased by 1 minute compared with ETT-1, the patient was considered to have completed the first qualifying ETT. If the decrease in time to onset angina was not ≥ 1 minute, a second antianginal drug could be withdrawn and the above sequence repeated. If necessary, a third antianginal drug could be withdrawn according to this procedure in order for the patient to qualify. Long-acting nitrates were always withdrawn first; beta-blockers; and calcium antagonists could be withdrawn in either order from patients not receiving long-acting nitrates. After the patient achieved the first qualifying ETT (ETT-2), a second qualifying ETT (ETT-3) was performed in which the time to onset angina had to be within $\pm 15\%$ of that observed during ETT-2. In addition, each of the qualifying ETTs had to have ECG signs of ischemia (≥ 1 mm horizontal or down-sloping ST-segment depression in 3 consecutive beats). Patients meeting these criteria were used in the study.

After each 1 week period, patients returned to the exercise laboratory in the morning, at least 1 hour after a light breakfast, for an ETT. This was designated the trough ETT; the trough ETTs were performed at the same time of day for each patient. After completing the trough ETT, the patient received the next scheduled blinded medication dose from the blister pack used that week. Another ETT was performed 1 hour after the administered dose. This was designated the peak ETT. Blood samples were obtained at trough (approximately 8 hours after dosing) and at peak (1 hour after dosing). Other standard laboratory tests were monitored regularly throughout the study.

Blood pressure (by cuff) and heart rate were monitored before all ETTs, during the ETT, during the last minute of each stage of the test, at onset angina, at the point of maximum exercise, and during recovery (every minute for 4 minutes, then every 5 minutes until values returned to baseline). Heart rates also was monitored continuously and standard 12-lead ECG recordings were done immediately before exercise with the patient standing on the treadmill, at the end of each stage of exercise, at the maximally tolerated exercise load, and at the termination of exercise.

Mean treadmill exercise times for the 3 exercise variables of interest during placebo and the different ranolazine dosing regimens (ranolazine-placebo) for all patients at peak and trough are summarized in Table 2 below.

Table 2
Exercise Test Data for All Patients at Peak and Trough

Mean Exercise Variable (all patients, minutes)	Treatment				
		Double-blind Placebo	Ranolazine 400 mg bid	Ranolazine 267 mg tid	Ranolazine 400 mg tid
Time to onset angina	Peak	9.01	9.33	9.40	9.33
	Trough	8.58	8.77	8.78	8.65
Exercise Duration	Peak	10.67	10.83	10.87	10.84
	Trough	10.50	10.55	10.56	10.60
Time to 1 mm ST depression	Peak	9.58	9.86	9.99	9.94
	Trough	9.04	9.22	9.22	9.31

At peak ranolazine plasma concentrations, all ETT ischemia parameters were prolonged over placebo and most notably, the time to onset of 1-mm ST-segment depression.

In the all-patients analysis, the increase in time to onset angina over placebo ranged from 0.32 to 0.39 minutes ($p \leq 0.01$) and time to onset of 1-mm ST-segment depression ranged from 0.28 to 0.41 minutes ($p \leq 0.02$) for each of the 3 ranolazine dosing regimens and all regimens combined. Also, the total duration of exercise was significantly increased for all regimens combined and trends of similar direction and magnitude were noted for each dosing regimen. In the per-protocol analysis each of the 3 ETT parameters were prolonged ($p \leq 0.01$) for all ranolazine dosing regimens combined. All individual ranolazine dosing regimens significantly prolonged time to 1-mm ST-segment depression and nonsignificant trends of similar direction and proportions were found for time to onset angina and duration of exercise. In general, results of the per-protocol analysis, except that the magnitude of the effect appeared to somewhat greater in those with monotherapy.

At trough plasma concentrations, ranolazine had a lesser effect on ETT parameters. The results for the all-patients and per-protocol analyses were relatively consistent, demonstrating trends to increased exercise times. But only the time to 1 mm ST-segment depression for all ranolazine regimens combined in the all-patients analysis achieved statistical significance.

In view of the more pronounced increases in exercise parameters observed with ranolazine monotherapy, the responses to ranolazine among patients receiving different concomitant antianginal medications were analyzed. These post-hoc analyses were performed on peak ranolazine data, when the effects to improve exercise times were most evident. Because long-acting nitrates were withdrawn first during the single-billed qualifying phase, no patient entered double-blind treatment receiving long-acting nitrates. Of patients with peak efficacy data, 34% (107/312) of the patients received beta-blockers during double-blind treatment and 24% (75/312) received calcium antagonists.

Exercise test parameters improved at peak ranolazine concentrations (ranolazine-placebo) whether or not patients were receiving beta-blockers. These improvements were slightly larger in magnitude in the 205 patients not receiving beta-blockers compared to the 107 patients who received beta-blockers. But the differences between those receiving beta-blockers and those not receiving them did not achieve statistical significance for any exercise parameter. In patients not receiving beta-blockers, all exercise parameters improved

significantly on each of the 3 ranolazine regimens, and also with all ranolazine regimens combined. Similar trends were observed in the smaller number of patients receiving beta-blockers. Analyses of exercise data from patients taking calcium antagonists compared with those not receiving calcium antagonists produced similar findings.

Table 3 below summarizes the mean peak and trough plasma ranolazine concentrations, in terms of ranolazine dihydrochloride base, for all patients by gender and for each dosing regimen.

Table 3
Mean (\pm Standard Deviation) Ranolazine Plasma Concentrations by Dosing Regimen

	Ranolazine 400 mg bid	Ranolazine 267 mg tid	Ranolazine 400 mg tid
Peak (ng/mL)			
All Patients	1882 (1094)	1346 (823)	2128 (1198)
Males	1762 (999)	1261 (774)	1917 (1046)
Females	2171 (1253)	1594 (904)	2654 (1385)
Trough (ng/mL)			
All Patients	235 (288)	316 (336)	514 (500)
Males	235 (264)	316 (336)	518 (494)
Females	235 (342)	316 (340)	505 (517)

The plasma mean peak concentrations ranged from 1346 to 2128 ng per mL ranolazine free base. The 400 mg tid dosing regimen was associated with the highest ranolazine plasma concentrations. Mean trough ranolazine plasma concentrations ranged from 235 to 514 ng per mL. Mean peak ranolazine plasma concentrations were somewhat higher in females than in males, but there were no sex differences in plasma concentrations evident in trough.

At peak ranolazine plasma concentrations, there were no statistically significant differences among any of the ranolazine dosing regimens and placebo for double product. Likewise, at trough ranolazine plasma concentrations, there were no statistically significant differences among the 3 ranolazine dosing regimens and placebo in the per-protocol analysis for standing or maximum exercise double product.

The results of this study suggest that ranolazine is an effective antianginal and anti-ischemic compound in patients with chronic stable angina pectoris. At peak plasma concentrations, the three ranolazine dosing regimens used prolonged time to onset of angina and duration of exercise as well as time to 1-mm ST-segment depression on average about 0.33 minutes over that observed with placebo. Improvement in exercise parameters was

observed in the present study not only in patients receiving concomitant antianginal therapy (eg, beta-blockers and calcium antagonists), but also in the subgroup who received only ranolazine monotherapy. In the latter patients, the treatment effect appeared to be somewhat greater in magnitude. This suggests that ranolazine also may be useful in monotherapy in patients with chronic stable angina pectoris.

The hemodynamic findings indicate that the improvement in exercise parameters in peak ranolazine plasma concentrations was not associated with changes in blood pressure or heart rate. The nonhemodynamic mechanism of action of ranolazine, therefore, differs from that of other antianginal drugs in current clinical use.

Most important, we documented that the antianginal and anti-ischemic effects of the immediate-release ranolazine preparation studied did not persist throughout the dosing interval. Although time to onset of ischemic-type ST-segment depression was significantly prolonged and trends of similar direction were noted for other ETT parameters, the effect was minimal at trough ranolazine plasma concentrations. Mean peak ranolazine free base plasma concentrations ranged from 1346 to 2128 ng per mL, while mean trough plasma concentrations ranged from 235 to 514 ng per mL. It seems evident that the higher mean ranolazine plasma concentrations observed at peak are associated with clinically meaningful antianginal and anti-ischemic effects, whereas concentrations obtained at trough were not.

Based on the results of the present experiment, the threshold plasma ranolazine free base concentration for anti-ischemic activity detected during ETT is likely to lie above about 550 ng per mL. Further, it is likely that ranolazine plasma concentrations must be maintained at or above the threshold value throughout the dosing interval to ensure antianginal and anti-ischemic activity during exercise throughout this interval.

Ranolazine was well tolerated over the plasma concentrations achieved in the present study. The rate of occurrence of adverse events did not differ among the ranolazine dosing regimens and placebo, and there were no drug-related changes in ECG intervals or complex morphology. In addition, there were no clinically significant changes in blood glucose concentrations, lipid values or liver function tests, suggesting that the metabolic effect of ranolazine does not extend to systemic glucose regulation or lipid metabolism.

Ranolazine improves exercise parameters with no detectable effect on heart rate and blood pressure in patients with chronic stable angina pectoris. It is likely that a threshold ranolazine plasma concentration above about 550 ng per mL must be obtained to detect these

antianginal and anti-ischemic effects. Ranolazine is well tolerated over a wide range of plasma concentrations. Further study using larger doses of a sustained release preparation are warranted to fully evaluate this novel metabolic concept for management of ischemia.

EXAMPLE 4

I. *In vitro* Comparison of IR Formulation and SR Formulations

The IR Formulation prepared according to Example 1 and the SR Formulations prepared according to Examples 2A-2C were tested in a USP Apparatus 2 dissolution tester, using 900 mL of 0.1M hydrochloric acid as the dissolution fluid to simulate dissolution in the stomach.

Table 4

Time (hours)	Percentage of Formulation Dissolved			
	Formulation			
	IR	A	B	C
0.25	88.1			
0.5	100.5	13.9	17.6	17.5
1	101.7	19.9	26.0	25.7
2		27.8	47.5	35.9
4		39.0	69.2	48.4
8		52.4	90.1	64.7
12		61.6	99.6	74.2
24		80.8	105.6	95.4

The tabular results show that while the IR Formulation is completely dissolved in no more than 0.5 hours (as expected for an immediate release formulation), SR Formulations A, B, and C displayed a prolonged dissolution of a low pH, as is desirable for a sustained release formulation.

II. *In vivo* Comparison of IR Formulation and SR Formulations A, B, and C

Single doses of the IR Formulation prepared according to Example 1 and SR Formulations A and B prepared according to Example 2 were administered to eleven healthy volunteers and their plasma concentrations of ranolazine free base were measured at 0, 20, 40, 60, 90, and 120 minutes, hourly to six hours, twice-hourly to eighteen hours, and at twenty-

four hours after administration (SR Formulations only). The results are set forth in Table 5 below.

Table 5
Formulation

	IR	A	B	C
C_{max} (ISD) (ng/mL)	1940 (807)	753 (264)	657 (316)	925 (747)
C_{trough} (ISD) (ng/mL)	165 (111)	158 (114)	182 (110)	290 (163)
T_{max} (ISD) (hours)	1.27 (0.5)	4.09 (1.14)	4.05 (1.31)	6.55 (2.93)
AUC_{0-24} (ISD) (ng.hr/mL)	6530	5640	5280	5820

From Table 5 it is apparent that SR Formulations A, B and C of this invention exhibit dissolution properties which make them suitable for twice daily administration of ranolazine.

EXAMPLE 5

This Example details a single-ascending dose, crossover-design study that assessed the safety and pharmacokinetic profile of single oral dose of ranolazine base SR Formulation of Example 2D. Human subjects were divided into three groups. Group 1 received 500, 750 and 1000 mg ranolazine SR. Group 2 received 1250 and 1750 mg ranolazine SR. Group 3 received 1500 and 2000 mg ranolazine SR. Each group also had a randomized placebo phase. Mean pharmacokinetic parameters following single oral doses of the ranolazine SR does are detailed in Table 6 below:

Table 6

Mean \pm SD Pharmacokinetic Parameters (n = 8 except* n = 7)					
Dose SR (mg)	Group	C_{max} (ng/mL)	C_{trough} (ng/mL)	T_{max} (hr)	AUC_{0-30h} (ng.hr/mL)
500	1	883 \pm 353	382 \pm 251	4.63 \pm 1.19	9380 \pm 4250
750	1	1300 \pm 1060	455 \pm 353	4.25 \pm 0.886	12500 \pm 9000
1000	1*	1610 \pm 959	695 \pm 438	5.71 \pm 2.14	18100 \pm 9630
1250	2	2210 \pm 716	943 \pm 541	6.21 \pm 3.52	25000 \pm 8090
1500	3	1980 \pm 1050	1070 \pm 754	4.75 \pm 0.886	25400 \pm 16000
1750	2	3670 \pm 1570	2400 \pm 1260	5.25 \pm 2.31	49200 \pm 18200
2000	3	2440 \pm 1120	1640 \pm 937	5.21 \pm 2.30	35400 \pm 19100

The pharmacokinetic results reported in Table 6 indicate that ranolazine was slowly released from the SR formulation, and consequently the absorption of ranolazine was dissolution-rate limited. This resulted in prolonged plasma drug concentration-time profiles observed at all dose levels, with peak plasma levels at 4 to 6 hours post dose. Over the dose range 500 to 2000 mg, the mean C_{\max} and $AUC_{0-30\text{hr}}$ increased in an approximately dose-proportional manner, although there appeared to be some deviation from proportionality within Group 2.

EXAMPLE 6

This Example details a double-blind, placebo-controlled, multiple ascending-dose, crossover-designed volunteer study, to evaluate bid dosing. Six subjects received 4 days dosing with ranolazine SR formulation prepared according to Example 2D at 500, 750, and 1000 mg bid, followed by a morning dose on Day 5. Pharmacokinetic results are reported in Table 7, below.

Table 7

Day 5 Ranolazine Pharmacokinetic Parameters (mean \pm SD)			
Parameter	Ranolazine SR 500 mg bid (n=7)	Ranolazine SR 750 mg bid (n=7)	Ranolazine SR 1000 mg bid (n=7)
C_{max} (ng/mL)	1760 \pm 715	2710 \pm 657	3660 \pm 1090
T_{max} (hr)	2.00 \pm 1.15	4.33 \pm 1.62	4.17 \pm 2.48
C_{min} (ng/mL)	585 \pm 340	1260 \pm 501	1960 \pm 812

According to Table 7, ranolazine was slowly released from the SR formulation, and consequently the pharmacokinetics were dissolution-rate limited. This resulted in extended plasma drug concentration-time profiles at all dose levels, with peak plasma levels observed at 2 to 4 hours post dose.

These results indicate that useful ranolazine plasma levels can be achieved in humans with dosing of this SR formulation on a bid schedule.

Example 7**Monotherapy Assessment of Ranolazine in Stable Angina (MARISA)**

MARISA is the first study of sustained release ranolazine (SR) in stable angina.

Background: Ranolazine (Ran) is a partial inhibitor of fatty acid oxidation (pFOX inhibitor). Shifting ATP production away from fatty acid oxidation toward carbohydrate oxidation, Ran reduces oxygen demand without decreasing cardiac work, and maintains coupling of glycolysis to pyruvate oxidation, which minimizes lactate accumulation. In three earlier placebo-controlled stable angina studies, oral Ran (immediate release) at ≥ 240 mg, alone or in combination with other anti-anginals, increased exercise times without changes in rest or exercise heart rates or decreases in rest or exercise blood pressures. In these earlier trials, statistically significant increases in exercise times occurred only near peak Ran plasma levels (1-3 hr after dosing). This investigation evaluates sustained-release (SR) formulations

to determine if the formulations can keep plasma levels in a therapeutic range with bid dosing.

Methods: Patients withdrawn from other anti-anginal drugs with reproducible angina-limited exercise duration and ≥ 1 mm ST depression were randomized to Ran (500 mg bid, 1000 mg bit and 1500 mg bid) and matching placebo (Pbo) in a double-blind, four-period, Latin square crossover design. Exercise testing with a modified Bruce protocol was performed at both trough (12 hr after dosing) and peak (4 hr after dosing). Results: 49 centers in the USA, Czech Republic, Poland and Canada randomized 191 patients. 168 completed all 4 double-blind treatment periods; 7 more completed 3 of 4 periods. These 175 patients were included in the primary analysis of efficacy, shown in Table 8 below.

Table 8

	Placebo		500 mg bid		1000 mg bid		1500 mg bid	
	trough	peak	Trough	Peak	trough	peak	trough	peak
Exercise Duration (sec)	511	504	533	532	545	555	559	561
p-value vs. placebo	-	-	0.003	<0.001	<0.001	<0.001	<0.001	<0.001
Time to Angina (sec)	412	418	437	452	457	474	472	487
p-value vs. placebo	-	-	0.005	<0.001	<0.001	<0.001	<0.001	<0.001
Time to 1 mm ST Depression (sec)	448	442	470	479	491	502	514	508
p-value vs. placebo	-	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Results: Ran improved exercise duration times in comparison to the placebo. Plasma peak and trough concentrations are reported in Table 9 below. Ran had no clinically meaningful effects vs. Pbo on rest or exercise blood pressure or heart rate.

Table 9

MARISA Study Results
Ranolazine Plasma Concentration
Mean (\pm standard deviation) by dose

Dose	500 mg BID	1000 mg BID	1500 mg BID
Peak (ng/mL)	1122 (727)	2461 (1525)	3935 (2084)
Trough (ng/mL)	846 (651)	1949 (1425)	3266 (1973)

From Table 9, it appears that plasma Ran concentration levels of at about 850 ng/mL or greater and up to at least 4000 ng base/mL provide beneficial results.

Example 8

5 In this Example, ranolazine (Ran) was administered to two sets of human subjects. The first set of subjects were suffering from angina alone while the second set of subjects were suffering from angina and diabetes.

10 The MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) study randomized patients to Ran (500 mg, 1000 mg and 1500 mg bit) and placebo in a double-blind, 4 period crossover study. All patients performed a modified Bruce exercise test at the time of trough and peak drug levels on each treatment; 42 patients with DM were compared to 133 non-DM patients.

15 Exercise duration (ED; see Table 10, below), time to angina and time to 1 mm ST depression were prolonged by Ran at both peak and trough (treatment p-values <0.001) and generally increased with dose. At peak and trough, Ran effects were similar in diabetic (DM) DM and non-DM patients (treatment by DM interaction p-values >0.05). In DM patients, at least one adverse event occurred in 16%, 23%, 23% and 33% of patients on placebo, 500 mg, 1000 mg and 1500 mg, respectively; in non-DM patients the analogous values were 15%, 13%, 21% and 34%, respectively. Mean changes (\pm SE) from baseline to the end of the study
20 in glucose and triglyceride levels were similar between DMs and non-DMs (glucose; DMs 10 ± 11 mg/dL, non-DMs 3 ± 2 mg/dL [NS]; triglycerides: DMs 10 ± 17 , non-DMs -7 ± 6 mg/dL [NS]).

Patients with chronic angina and DM appear to tolerate and to respond to Ran, a pFOX inhibitor, as well as patients without DM.

Table 10

LS mean ED (Sec)	Placebo		Ran 500 mg bid		Ran 1000 mg bid		Ran 1500 mg bid	
	trough	peak	Trough	peak	trough	peak	trough	peak
DM n=42	499	498	520	527	526	550	530	547
Non- DM n=133	503	500	528	530	539	550	544	557

Treatment p-values; trough <0.001; peak<0.001

5 Treatment by DM interaction p-values; trough=0.768; peak=0.953

Example 9

This Example evaluates the effectiveness of ranolazine (Ran) in human patients with chronic angina and a history of heart failure.

10 The MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) study randomized patients to Ran (500 mg, 1000 mg and 1500 mg bid) and placebo in a double-blind, 4 period, crossover design study. 29 patients had a history of heart failure (HF) and 146 did not. All patients performed a modified Bruce exercise test at the time of trough (morning) and peak (afternoon) drug levels on each treatment.

15 Exercise duration (ED; see Table 11, below), time to angina and time to 1 mm ST segment depression (TtSTD) were prolonged by Ran at peak and trough (treatment p-values<0.001) and increased with dose. At trough, Ran effects were similar in pts with and without HF (treatment by HF interaction p-values > 0.05). ED in HF pts fell between morning trough and afternoon peak testing on placebo, in contrast to pts without HF. At peak, increases on
20 Ran in ED and TtSTD were greater in HF pts than in those without (treatment by HF interaction p-values 0.01 and 0.007, respectively), reversing the fall between trough and peak in exercise performance in HF. HF patients did not have more adverse events than those without HF. Ran did not change rest or exercise heart rate or systolic blood pressure.

25 Patients with chronic angina and a history of HF appear to tolerate and to respond to Ran, a pFOX inhibitor, at least as well as those without HF.

Table 11

LS mean ED (Sec)	Placebo		Ran 500 mg bid		Ran 1000 mg bid		Ran 1500 mg bid	
	trough	peak	trough	peak	trough	peak	trough	peak
HF n=29	482	442	512	518	514	520	524	545
No HF n=146	517	518	539	538	551	563	563	564

Treatment p-values; trough <0.001; peak <0.001

Treatment by HF interaction p-values; trough=0.939; peak=0.01

Example 10

5 This Example evaluates the ability of ranolazine to reduce myocardial infarct size.

The aim of this study was to investigate whether ranolazine exerts beneficial effects in a rat model of regional myocardial ischemia and reperfusion.

Methods: Male Wistar rats were subjected to no LAD-occlusion (sham) or LAD-occlusion (25 min) and reperfusion (2 h). Saline (bolus: 2.4 mL/kg+ infusion: 24. mL/kg/h) or ranolazine (bolus: 10 mg/kg + infusion; 96. mg/kg/h) were infused 30 min before LAD-occlusion and throughout the experiment. At the end of the experiment area at risk (AR, % of left ventricle), infarct size (IS, % of AR), and plasma cardiac troponin T (cTnT, ng/mL) were determined.

15 The following groups were studied: Group 1. sham saline (n=4), Group 2. saline control (n=12), Group 3. ranolazine (n=12).

Results are expressed as mean±SEM; P<0.05 vs. saline control (group 2). ANOVA+Bonferroni. Group 1: AR=47±3, IS=<3=, cTnT=<0.1=Group 2: AR=48±2, IS=61±2, cTnT=65±14 Group 3: AR=48±1, IS=41±5, cTnT=12±2.

20 These results demonstrate for the first time that ranolazine significantly reduces (1) infarct size and (2) cTnT release in rats subjected to LAD-occlusion and reperfusion.

What is claimed is:

1. A method for treating a mammal suffering from angina and at least one second disorder by administering a dose of a pharmaceutical dosage form to the mammal including ranolazine and at least one pharmaceutical excipient.
- 5 2. The method of claim 1 wherein the pharmaceutical dosage form is solid dosage form and the dose is at least one dosage form.
3. The method of claim 2 wherein the dose is no more than two dosage forms wherein the dosage forms are selected from capsules and tablets.
4. The method of claim 1 wherein the dose is administered at a frequency
10 selected from once, twice and three times over 24 hours.
5. The method of claim 1 wherein the mammal is a human.
6. The method of claim 1 wherein the ranolazine is administered for an period of time that exceeds one week.
7. The method of claim 1 wherein the dose includes a sufficient amount of
15 ranolazine to maintain a plasma ranolazine level that does not drop below 850 ng base/mL during a 24 hour period of time.
8. The method of claim 1 wherein the maximum plasma ranolazine level is about 4000 ng base/mL.
9. The method of claim 1 wherein the pharmaceutical dosage form includes
20 between about 50% to about 95% by weight ranolazine.
10. The method of claim 1 wherein the pharmaceutical dosage form includes from about 70% to about 80% by weight ranolazine.
11. The method of claim 1 wherein the peak to trough human patient plasma ranolazine levels is less than 4:1 over a 24 hour period.
- 25 12. The method of claim 1 wherein the peak to trough human patient plasma ranolazine levels is less than 3:1 over a 24 hour period.
13. The method of claim 1 wherein the dose includes from about 500 to 1500 mg ranolazine.
14. The method of claim 1 wherein the second disorder is heart disease.
- 30 15. The method of claim 1 wherein the second disorder is diabetes.
16. A method for reducing myocardial infarct size in a mammal by administering a dose of a pharmaceutical dosage form to the mammal including ranolazine and at least one

pharmaceutical excipient.

17. The method of claim 16 wherein the dose is administered before the mammal experiences an ischemic event.

18. The method of claim 17 wherein the route of administration is oral and
5 wherein the dosage form is a solid dosage form including from about 0.01 to about 50 mg/kg/day ranolazine.

19. The method of claim 16 wherein the dose is administered at a time selected from the group consisting of as the mammal is experiencing an ischemic event and following an ischemic event.

10 20. The method of claim 19 wherein the dose is administered intravenously or by bolus.

21. The method of claim 20 wherein the dosage form is a liquid.

22. The method of claim 16 wherein the mammal is a human.

15

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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
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(54) Title: METHOD FOR TREATING ANGINA

(57) Abstract: A method for administering a ranolazine dosage formulations to treat patients suffering from angina who are also suffering from a second complication or disease such a heart disease and diabetes and also to reduce myocardial infarct size wherein the infarcts is the result of an ischemic event.

WO 02/07716 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/22957

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, CHEM ABS Data, MEDLINE, EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZACHAROWSKI KAI ET AL: "Ranolazine reduces myocardial infarct size and cardiac Troponin T release in the anaesthetised rat." BRITISH JOURNAL OF PHARMACOLOGY, vol. 131, no. Proceedings Supplement, October 2000 (2000-10), page 25P XP001058441 Meeting of the British Pharmacological Society; Cardiff, Wales, UK; July 12-14, 2000 ISSN: 0007-1188 abstract --- -/--	1-14, 16-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

17 January 2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/22957

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 00 13687 A (CV THERAPEUTICS INC ;WOLFF ANDREW A (US)) 16 March 2000 (2000-03-16) abstract; claims 1-30; examples 3,4 page 3, line 1 -page 5, line 25 ---	1-22
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/22957

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>STANLEY W C ET AL: "REGULATION OF MYOCARDIAL CARBOHYDRATE METABOLISM UNDER NORMAL AND ISCHAEMIC CONDITIONS POTENTIAL FOR PHARMACOLOGICAL INTERVENTIONS" CARDIOVASCULAR RESEARCH, XX, XX, vol. 33, no. 2, February 1997 (1997-02), pages 243-257, XP000978213 ISSN: 0008-6363 abstract page 249, column 2, paragraph 2 -page 250, column 2, paragraph 4 page 252, column 1, paragraph 4 -page 253, column 1, paragraph 2; figure 4</p>	1-22
X	<p>PEPINE C J ET AL: "A CONTROLLED TRIAL WITH A NOVEL ANTI-ISCHEMIC AGENT, RANOLAZINE, IN CHRONIC STABLE ANGINA PECTORIS THAT IS RESPONSIVE TO CONVENTIONAL ANTIANGINAL AGENTS" AMERICAN JOURNAL OF CARDIOLOGY, CAHNS PUBLISHING CO., NEWTON, MA., US, vol. 84, no. 1, 1 July 1999 (1999-07-01), pages 46-50, XP001016311 ISSN: 0002-9149 abstract</p>	1-22
P, X	<p>DEQUATTRO V ET AL: "COMPARATIVE ANTIANGINAL EFFICACY AND TOLERABILITY OF RANOLAZINE IN DIABETIC AND NONDIABETIC PATIENTS: RESULTS OF THE MARISA TRIAL" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, XX, XX, vol. 37, February 2001 (2001-02), page 338A XP001016314 ISSN: 0735-1097 abstract</p>	1-22
X	<p>US 4 567 264 A (KLUGE ARTHUR F ET AL) 28 January 1986 (1986-01-28) cited in the application abstract; examples 10-17</p>	1-22

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Present claims 1-13 relate to an extremely large number of possible uses. In fact, the claims contain so many options as far as relating to "at least one second disorder" that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely relating to the second disorder as being the disorders specified in claims 14,15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/22957

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